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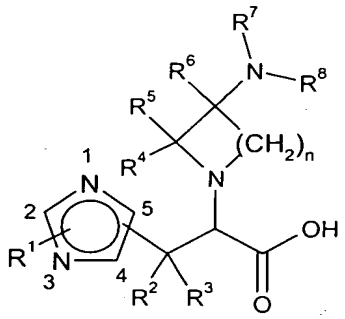
Claims

1 A compound according to formula (I)



(I)

wherein:

n is 1, 2, 3 or 4;

R^1 is selected from

a. an optionally substituted straight chain or branched chain C_{1-6} alkyl group,

b. an optionally substituted straight chain or branched chain C_{2-6} alkenyl group,

c. an optionally substituted straight chain or branched chain C_{2-6} alkynyl group,

d. Aryl,

e. Aromatic heterocycle,

f. Heterocycle, and

g. hydrogen;

where the optional substituents in groups (a), (b) and (c) above are selected from: C_{3-7} cycloalkyl, Aryl, Aromatic heterocycle, Heterocycle, OR^9, NR^9R^{10}, $S(O)_pR^9$, $OC(O)R^{10}$, CO_2R^9, $CONR^9R^{10}$, $SO_2NR^9R^{10}$, halo and $NHSO_2R^9$, and where p is 0, 1 or 2;

R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each independently selected from hydrogen and straight chain or branched chain C_{1-6} alkyl optionally substituted by OR^9 or halo;

R^9 and R^{10} are each independently selected from hydrogen and straight chain or branched chain C_{1-6} alkyl;

Aryl is a 6-14 membered aromatic monocyclic or fused polycyclic carbocyclic group optionally substituted with one or more groups selected from R^{11}, halo, OR^{12}, $NR^{12}R^{13}$, $NR^{12}CO_2R^{11}$, CO_2R^{12}, $NR^{12}SO_2R^{11}$, CN, haloalkyl, O(haloalkyl), SR^{12}, $S(O)R^{11}$, SO_2R^{11}, $OC(O)R^{12}$, $SO_2NR^{12}R^{13}$ and $C(O)NR^{12}R^{13}$, where R^{11} is straight chain or branched chain C_{1-6} alkyl and R^{12} and R^{13} are each independently selected from hydrogen and straight chain or branched chain C_{1-6} alkyl;

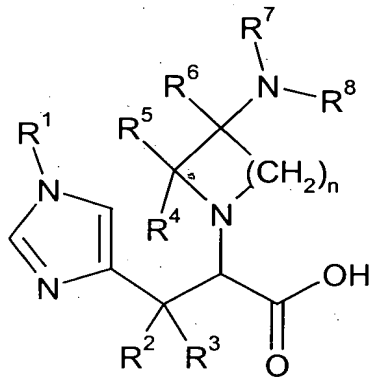
Aromatic heterocycle is a 5 to 7 membered aromatic ring containing from 1 to 3 heteroatoms, each independently selected from O, S and N, said ring being optionally substituted with one or more groups selected from OR^{12}, $NR^{12}R^{13}$, CO_2R^{12}, $NR^{12}CO_2R^{11}$, R^{11},

halo, CN, haloalkyl, O(haloalkyl), SR^{12}, $S(O)R^{11}$, SO_2R^{11}, $OC(O)R^{12}$, $NR^{12}SO_2R^{11}$, $SO_2NR^{12}R^{13}$ and $C(O)NR^{12}R^{13}$; and

Heterocycle is a 3 to 8 membered ring containing from 1 to 3 heteroatoms, each independently selected from O, S and N, said ring being saturated or partially saturated, said ring further being optionally substituted with one or more groups selected from OR^{12}, $NR^{12}R^{13}$, CO_2R^{12}, $NR^{12}CO_2R^{13}$, R^{11}, halo, CN, haloalkyl, O(haloalkyl), SR^{12}, $S(O)R^{11}$, SO_2R^{11}, $OC(O)R^{12}$, $NR^{12}SO_2R^{11}$, $SO_2NR^{12}R^{13}$ and $C(O)NR^{12}R^{13}$,

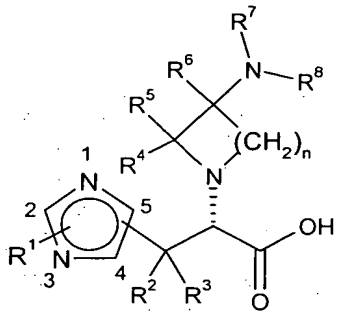
or a tautomer thereof, or a pharmaceutically acceptable salt or solvate of said compound or said tautomer.

2 A compound according to claim 1 wherein the substitution pattern of the imidazole is as depicted in formula (ID^1)



(ID^1)

3 A compound according to Claim 1 wherein the stereochemistry is as depicted in formula (IA)



(IA)

4 A compound according to any preceding Claim wherein n is 2 or 3.

5 A compound according to Claim 4 wherein n is 2.

6 A compound according to any preceding Claim wherein R^1 is hydrogen, Aryl or C_{1-6} alkyl optionally substituted by C_{3-7} cycloalkyl or Aryl.

7 A compound according to Claim 6 wherein R^1 is hydrogen, Aryl or C_{1-6} alkyl optionally substituted by cyclohexyl or Aryl.

8 A compound according to Claim 7 wherein R^1 is hydrogen, phenyl, C_{1-5} alkyl or C_{1-3} alkyl substituted by cyclohexyl or phenyl.

9 A compound according to Claim 7 wherein R^1 is hydrogen, Aryl or propyl.

10 A compound according to Claim 8 or Claim 9 wherein R^1 is propyl.

11 A compound according to any preceding Claim wherein R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are each independently hydrogen or C_{1-3} alkyl.

12 A compound according to Claim 11 wherein R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are all hydrogen.

13 A compound according to Claim 1, selected from:

(+)-(2*S*)-2-[(3*S*)-3-aminopyrrolidinyl]-3-(1*H*-imidazol-4-yl)propanoic acid;

(+)-(2*S*)-2-[(3*S*)-3-aminopyrrolidinyl]-3-(1-propyl-1*H*-imidazol-4-yl)propanoic acid;

(2*S*)-2-[(3*S*)-3-aminopyrrolidinyl]-3-(1-isopentyl-1*H*-imidazol-4-yl)propanoic acid;

(+)-(2*S*)-2-[(3*S*)-3-aminopyrrolidinyl]-3-[1-(2-cyclohexylethyl)-1*H*-imidazol-4-yl]propanoic acid;

(+)-(2*S*)-2-[(3*S*)-3-aminopyrrolidinyl]-3-[1-(2-phenylethyl)-1*H*-imidazol-4-yl]propanoic acid; and

(+)-(2*S*)-2-[(3*S*)-3-aminopyrrolidinyl]-3-[1-phenyl-1*H*-imidazol-4-yl]propanoic acid,

and pharmaceutically acceptable salts thereof.

14 A compound according to any of Claims 1 to 12 for use as a medicament.

15 A compound according to any of Claims 1 to 12 for use as a medicament for the treatment of a condition selected from thrombotic conditions, atherosclerosis, adhesions, dermal scarring, cancer, fibrotic conditions, inflammatory diseases and those conditions which benefit from maintaining or enhancing bradykinin levels in the body.

16 A pharmaceutical composition comprising a compound according to any of Claims 1 to 13 and a pharmaceutically acceptable carrier.

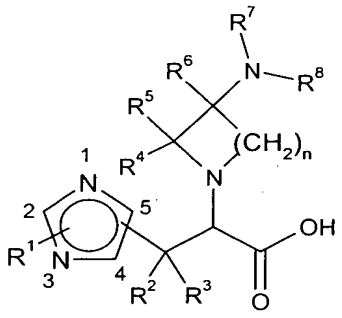
17 The use of a compound according to any of Claims 1 to 13 for the preparation of a medicament for the treatment of a condition selected from thrombotic conditions, atherosclerosis, adhesions, dermal scarring, cancer, fibrotic conditions, inflammatory diseases and those conditions which benefit from maintaining or enhancing bradykinin levels in the body.

18 A use according to Claim 17 wherein the medicament is for the treatment of a thrombotic condition.

19 A method of treatment of a condition selected from thrombotic conditions, atherosclerosis, adhesions, dermal scarring, cancer, fibrotic conditions, inflammatory diseases and those conditions which benefit from maintaining or enhancing bradykinin levels

in the body, comprising administration of a compound according to any of Claims 1 to 13 to a subject in need of such treatment.

A process for the preparation of a compound according to formula (I)



(I)

wherein:

n is 1, 2, 3 or 4;

R^1 is selected from

a. an optionally substituted straight chain or branched chain C_{1-6} alkyl group,

b. an optionally substituted straight chain or branched chain C_{2-6} alkenyl group,

c. an optionally substituted straight chain or branched chain C_{2-6} alkynyl group,

d. Aryl,

e. Aromatic heterocycle,

f. Heterocycle, and

g. hydrogen;

where the optional substituents in groups (a), (b) and (c) above are selected from: C_{3-7} cycloalkyl, Aryl, Aromatic heterocycle, Heterocycle, OR^9, NR^9R^{10}, $S(O)_pR^9$, $OC(O)R^{10}$, CO_2R^9, $CONR^9R^{10}$, $SO_2NR^9R^{10}$, halo and $NHSO_2R^9$, and where p is 0, 1 or 2;

R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each independently selected from hydrogen and straight chain or branched chain C_{1-6} alkyl optionally substituted by OR^9 or halo;

R^9 and R^{10} are each independently selected from hydrogen and straight chain or branched chain C_{1-6} alkyl;

Aryl is a 6-14 membered aromatic monocyclic or fused polycyclic carbocyclic group optionally substituted with one or more groups selected from R^{11}, halo, OR^{12}, $NR^{12}R^{13}$, $NR^{12}CO_2R^{11}$, CO_2R^{12}, $NR^{12}SO_2R^{11}$, CN, haloalkyl, O(haloalkyl), SR^{12}, $S(O)R^{11}$, SO_2R^{11}, $OC(O)R^{12}$, $SO_2NR^{12}R^{13}$ and $C(O)NR^{12}R^{13}$, where R^{11} is straight chain or branched chain C_{1-6} alkyl and R^{12} and R^{13} are each independently selected from hydrogen and straight chain or branched chain C_{1-6} alkyl;

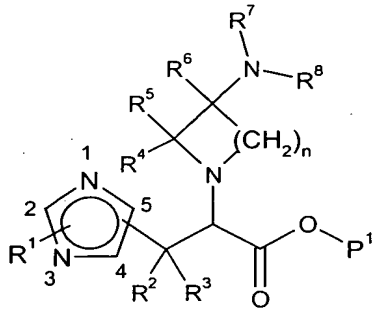
Aromatic heterocycle is a 5 to 7 membered aromatic ring containing from 1 to 3 heteroatoms, each independently selected from O, S and N, said ring being optionally

substituted with one or more groups selected from OR^{12}, $NR^{12}R^{13}$, CO_2R^{12}, $NR^{12}CO_2R^{11}$, R^{11}, halo, CN, haloalkyl, O(haloalkyl), SR^{12}, $S(O)R^{11}$, SO_2R^{11}, $OC(O)R^{12}$, $NR^{12}SO_2R^{11}$, $SO_2NR^{12}R^{13}$ and $C(O)NR^{12}R^{13}$; and

Heterocycle is a 3 to 8 membered ring containing from 1 to 3 heteroatoms, each independently selected from O, S and N, said ring being saturated or partially saturated, said ring further being optionally substituted with one or more groups selected from OR^{12}, $NR^{12}R^{13}$, CO_2R^{12}, $NR^{12}CO_2R^{13}$, R^{11}, halo, CN, haloalkyl, O(haloalkyl), SR^{12}, $S(O)R^{11}$, SO_2R^{11}, $OC(O)R^{12}$, $NR^{12}SO_2R^{11}$, $SO_2NR^{12}R^{13}$ and $C(O)NR^{12}R^{13}$,

or a tautomer thereof, comprising the steps of:

(i) preparing a compound according to formula (II)



(II)

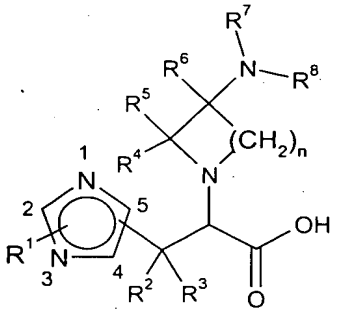
wherein:

P^1 is an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{4-7} cycloalkyl group, an optionally substituted benzyl group or a tri(C_{1-6} alkyl)silyl group; and

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and n are as defined for formula (I); and

(ii) treating said compound of formula (II) with a reagent or combination of reagents suitable for removing the P^1 group.

21 A process for the preparation of a compound according to formula (I)



(I)

wherein:

n is 1, 2, 3 or 4;

R^1 is selected from

a. an optionally substituted straight chain or branched chain C_{1-6} alkyl group,

b. an optionally substituted straight chain or branched chain C_{2-6} alkenyl group,

c. an optionally substituted straight chain or branched chain C_{2-6} alkynyl group,

d. Aryl,

e. Aromatic heterocycle,

f. Heterocycle, and

g. hydrogen;

where the optional substituents in groups (a), (b) and (c) above are selected from: C_{3-7} cycloalkyl, Aryl, Aromatic heterocycle, Heterocycle, OR^9, NR^9R^{10}, $S(O)_pR^9$, $OC(O)R^{10}$, CO_2R^9, $CONR^9R^{10}$, $SO_2NR^9R^{10}$, halo and $NHSO_2R^9$, and where p is 0, 1 or 2;

R^2, R^3, R^4, R^5, R^6, and R^7 are each independently selected from hydrogen and straight chain or branched chain C_{1-6} alkyl optionally substituted by OR^9 or halo;

R^8 is hydrogen;

R^9 and R^{10} are each independently selected from hydrogen and straight chain or branched chain C_{1-6} alkyl;

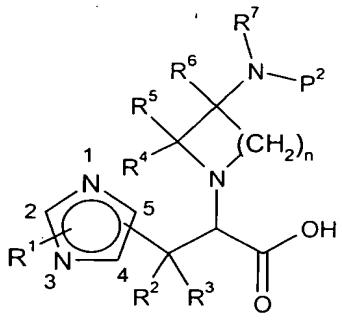
Aryl is a 6-14 membered aromatic monocyclic or fused polycyclic carbocyclic group optionally substituted with one or more groups selected from R^{11}, halo, OR^{12}, $NR^{12}R^{13}$, $NR^{12}CO_2R^{11}$, CO_2R^{12}, $NR^{12}SO_2R^{11}$, CN, haloalkyl, O(haloalkyl), SR^{12}, $S(O)R^{11}$, SO_2R^{11}, $OC(O)R^{12}$, $SO_2NR^{12}R^{13}$ and $C(O)NR^{12}R^{13}$, where R^{11} is straight chain or branched chain C_{1-6} alkyl and R^{12} and R^{13} are each independently selected from hydrogen and straight chain or branched chain C_{1-6} alkyl;

Aromatic heterocycle is a 5 to 7 membered aromatic ring containing from 1 to 3 heteroatoms, each independently selected from O, S and N, said ring being optionally substituted with one or more groups selected from OR^{12}, $NR^{12}R^{13}$, CO_2R^{12}, $NR^{12}CO_2R^{11}$, R^{11}, halo, CN, haloalkyl, O(haloalkyl), SR^{12}, $S(O)R^{11}$, SO_2R^{11}, $OC(O)R^{12}$, $NR^{12}SO_2R^{11}$, $SO_2NR^{12}R^{13}$ and $C(O)NR^{12}R^{13}$; and

Heterocycle is a 3 to 8 membered ring containing from 1 to 3 heteroatoms, each independently selected from O, S and N, said ring being saturated or partially saturated, said ring further being optionally substituted with one or more groups selected from OR^{12}, $NR^{12}R^{13}$, CO_2R^{12}, $NR^{12}CO_2R^{13}$, R^{11}, halo, CN, haloalkyl, O(haloalkyl), SR^{12}, $S(O)R^{11}$, SO_2R^{11}, $OC(O)R^{12}$, $NR^{12}SO_2R^{11}$, $SO_2NR^{12}R^{13}$ and $C(O)NR^{12}R^{13}$,

or a tautomer thereof, comprising the steps of:

(i) preparing a compound according to formula (IV)



(IV)

wherein:

P^2 is an (optionally substituted C_{1-6} alkyl)oxycarbonyl group, an (optionally substituted C_{4-7} cycloalkyl)oxycarbonyl group, an (optionally substituted benzyl)oxycarbonyl group or an (optionally substituted fluorenylmethyl)oxycarbonyl group; and

R^1, R^2, R^3, R^4, R^5, R^6, R^7 and n are as defined for formula (I); and

(ii) treating said compound of formula (II) with a reagent or combination of reagents suitable for removing the P^2 group.